The ACE trial: A randomized comparison of open versus endovascular repair in good risk patients with abdominal aortic aneurysm

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Endovascular repair of infrarenal abdominal aneurysms (EVAR) is currently used in patients with large aneurysm. Two randomized studies, Dutch Randomised Endovascular Aneurysm Management (DREAM) and Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1), showed favorable early results with EVAR; but at 2 and 4 years, the rates of all-cause mortalities were no longer different. Patients in EVAR groups required more reinterventions. These data were confirmed by national audits and large registries. However, there is still uncertainty concerning the durability of the devices, and long-term results are unknown. The ACE (Anevrysme de l'aorte abdominale, Chirurgie versus Endoprothese) trial is a multicenter, prospective randomized trial aimed at assessing the results of EVAR and of open surgery in relatively good-risk patients presenting with an asymptomatic abdominal aortic or aortoiliac aneurysm. The primary end point is death and major complications up to 5 years after randomization. Analysis of results is underway, and publication due by the end of the year. (J Vasc Surg 2009;50:222-4.)

Abdominal aortic aneurysm (AAA) rupture is a major cause of cardiovascular death in industrialized countries. Prophylactic repair is advised for large aneurysms in good- to moderate-risk patients. Although endovascular AAA repair (EVAR) is an attractive option because of its less invasive nature, there is still a room for uncertainty concerning its durability and overall long-term efficacy compared with open repair.

Two large randomized controlled trials, Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) and Dutch Randomised Endovascular Aneurysm Management (DREAM),[1,2] showed similar results. The EVAR-1 trial enrolled 1082 patients with a 30-day mortality of 1.7% after EVAR and 4.7% after open repair; the DREAM trial reported 1.2% mortality after EVAR and 4.6% after open repair. At 2 years for DREAM,[3,4] and 4 years for EVAR-1, the all-cause mortality was not different in the two arms. The aneurysm-related mortality was lower in the EVAR groups, but the rate of reinterventions was significantly higher.

National institutes around the world issued various recommendations. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) Committee concluded that endovascular stent grafts were an appropriate use of National Health Service resources. In other countries such as Canada, Belgium, and France, however, health care resource providers were more conservative and asked for more data and longer follow-up. In France, although the regulation may change soon, reimbursement is still limited to high-risk patients as defined by the Agence Française de Securité Sanitaire (AFSSAPS; Table I).

Table I. Current criteria for endovascular treatment of abdominal aortic aneurysm by stent graft legislation issued by the Agence Française de Securité Sanitaire (AFSSAPS) in 2003 and still valid in 2009

AFSSAPS criteria

- Abdominal aortic aneurysm >50 mm or growth >1 cm in 1 year
- Age >80 years old
- Coronaropathy defined by a past history of myocardial infarction, angina pectoris, positive functional tests, and coronary intervention (percutaneous transluminal angioplasty or coronary artery bypass grafting) not feasible or not indicated
- Cardiac insufficiency with clinical symptoms
- Noncorrectable tight aortic valve stenosis
- Left ventricular ejection fraction <40%
- Respiratory insufficiency defined by
  Forced expiratory ventilation in 1 second <1.2/s
  Vital capacity <50% of the predicted value
  $PaCO_2$ <45 mm Hg or PaO_2 <60 mm Hg
  Permanent oxygen therapy
- Serum creatinine >200 μmol
- Hostile abdomen

The main question remains the long-term durability of EVAR. Rupture after EVAR occurs, and it is still uncertain whether the early benefit of EVAR will not be reversed by better long-term results with open repair. Of concern is that the DREAM principal investigator stated in an oral presentation in November 2008 (personal communication, J. D. Blankensteijn, 2008) that EVAR may be associated with a higher mortality rate than open repair at 5 years. On

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the other hand, better clinical results are expected due to improved reliability of the most recent devices.

The ACE (Anevrysme de l'aorte abdominale, Chirurgie versus Endoprothèse) trial was conceived in 1998 when no level 1 evidence existed. ACE is a multicenter, prospective randomized trial to assess the results of EVAR and of open surgery in relatively healthy patients presenting with an asymptomatic abdominal aortic or aortoiliac aneurysm.

PROTOCOL

Inclusion criteria. Inclusion criteria combined anatomy and physical status assessment:

- Anatomic assessment was based on computed tomography (CT) scan evaluation. Patients were eligible when the AAA was >50 mm in men or >45 mm in women. The upper neck, calculated from the lower renal artery to the aneurysm sac, had to measure at least 15 mm in length and be free of major thrombus or of circular calcification. The angle between the axis of the aneurysm and the axis of the neck could not exceed 60°. The iliac arteries had to be large enough to be compatible with the introducer sheath. Bifurcated as well as aortouniiliac grafts could be used.
- Physical status assessment included age, cardiac, renal, and pulmonary evaluation according to the criteria of the Society for Vascular Surgery/American Association for Vascular Surgery comorbidity score.

Randomization. Data were collected by fax from the various centers at the Clinical Research Unit (URC) of Henri Mondor Hospital. After randomization by the center, arm allocation was notified ≤24 hours.

Follow-up. Patients were seen at 1, 6, and 12 months, and yearly thereafter for the duration of the study (minimum 1 year for each patient). In the EVAR arm, a contrast CT scan was performed at each interval, whereas in the open repair, group the scan was performed at the end of follow-up. Plain radiographs and duplex scans were also performed at each interval in the EVAR group. All events and surveillance data, including eventual rehospitalizations, were collected in the case report form.

End points. The primary end point was death of any cause and major adverse events, defined as myocardial infarction, permanent stroke, permanent hemodialysis, major (leg or thigh) amputation, paraplegia, bowel infarction, and reinterventions for graft replacement. Secondary end points included minor complications.

Statistical analysis. Statistical analysis will compare by log-rank test the actuarial survival and the freedom from major adverse events for the duration of the study in the two arms. Cox logistic regression analysis will evaluate the influence of prognosis parameters such as anatomic factors and risk factors.

Study organization and surveillance. Five committees were set up to organize and monitor the on-going study: a steering committee, a scientific committee, a committee for center selection, a committee for end points and adverse events validation, and a committee for safety issue. Each committee meets at regular intervals.

All data are monitored by comparing case report forms and data trial sheets to check for accuracy. End points are validated by a specific independent committee that consists of anesthesiologists, cardiologists, vascular surgeons, radiologists, and internists.

TRIAL UPDATE

The ACE protocol was approved by the Henri Mondor Hospital ethical committee in 1998 and is identified at the ClinicalTrials.gov identifier under the number NTC00224718. A grant of €600,000 was obtained from the Programe Hospitalier de Recherche Clinique (PHRC) of the Ministry of Health (MOH) in 1999, and was transferred to the Clinical Research Center for Délégation à la Recherche Clinique (DRC), which is in charge of the committee for end points and adverse events validation, the safety committee, the organization, and the data monitoring and analysis.

The grant alone could not cover the cost of the stent grafts and, since then, no reimbursement of the graft by Caisse Nationale d'Assurance Maladie (CNAM) [Social Security] has been available because the CNAM advocated that its role was not to fund research. The following solutions were found: in the public sector, grafts were purchased by the hospitals from their own budget, and firms provided a limited number of free grafts to the private sector.

Regulations were changed at the date the trial was expected to begin: the organization of the Agence Nationale d'Evaluation Médicale changed to become Agence Française de Sécurité Sanitaire Pour la Santé (the National Health Agency), and for >1 year, the use of any stent graft was forbidden until each device was assessed and approved by a specific committee. Then, insurance issues and agreements between administration of the various centers and the DRC added more delay. Finally, the very first patient was enrolled in 2003. Between 2003 and 2008, 25 vascular centers from university and private hospitals in France contributed to the study.

Randomization was slow for a variety of reasons: First, funding was lacking for the stent grafts.

Second, strict regulatory limitation of EVAR to high-risk patients by AFSSAPS, in which violating these limitations could mean fines and being forbidden to practice for 1 to several months. Although surgeons were covered within the framework of the study, many became reluctant to randomize good-risk patients.

Third, publication of the early results of DREAM and EVAR-1 trials in 2004 reduced the enthusiasm of some participating centers.

Given this evolution, the scientific committee decided to stop the enrollment by March 2008 and to extend the follow-up for 3 more years. So far, a cohort of 306 patients is being followed up, and data from 1 to 5 years are available. Most of collected data are now stored in a database and double-checking of the accuracy of the stored items is currently ongoing. The committee of end point

evaluation has already met several times, and data have been collected with a strict control of the concordance with patient's records. Interim analysis is due September 2009, with the initial publication by the end of 2009.

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INVITED COMMENTARY

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Several multicenter randomized trials have compared endovascular and open repair options in good-risk aneurysm patients, including the Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) and Dutch Randomised Endovascular Aneurysm Management (DREAM) European studies that reported an early survival advantage after endovascular repair. The Veterans Affairs Study in the United States (OVER) completed recruitment of 881 patients in April 2007 and results are expected soon.

The Anévrisme de l'aorte abdominale: Chirurgie versus Endoprothèse (ACE) study from France uses a similar study protocol and has completed recruitment of 306 patients. This report describes the challenges the French investigators have faced with regulatory bodies and funding agencies resulting in patient recruitment lagging 5 years after initial ethics approval. This environment may have contributed to the emergence of laparoscopic aortic surgery as a minimally invasive therapeutic option, which French surgeons have been pivotal in developing.

The ACE investigators should be commended for their perseverance in completing this study. One wonders, though, with 306 patients recruited whether we will see a repeat of the early DREAM results (345 patients), where the early survival advantage was similar to that achieved with EVAR-1 and was viewed as clinically significant, but failed to reach statistical significance. Regardless, we await the results, which should be interesting and valuable.